(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 October 2003 (30.10.2003)

PCT

(10) International Publication Number
WO 03/089412 A1

(51) International Patent Classification[7]: C07D 211/58, 401/06, 409/06, 405/06, 417/14, 401/14, 413/06, 417/06, 513/04, A61K 31/45, 31/4523, A61P 31/04

(21) International Application Number: PCT/GB03/01541

(22) International Filing Date: 9 April 2003 (09.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0208579.3 13 April 2002 (13.04.2002) GB

(71) Applicant *(for all designated States except US)*: **BRITISH BIOTECH PHARMACEUTICALS LTD** [GB/GB]; Watlington Road, Oxford OX4 6LY (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AYSCOUGH, Andrew, Paul** [GB/GB]; British Biotech Pharmaceuticals Ltd, Watlington Road, Oxford OX4 6LY (GB). **KEAVEY, Kenneth** [IE/GB]; British Biotech Pharmaceuticals Ltd, Waltington Road, Oxford OX4 6LY (GB).

(74) Agent: **WALLS, Alan, J.**; c/o British Biotech Pharmaceuticals Ltd, Watlington Road, Oxford OX4 6LY (GB).

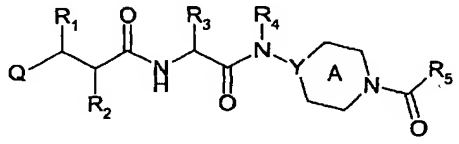
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

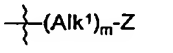
**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: ANTIBACTERIAL AGENTS



(II)



(IIA)

(57) Abstract: Compounds of formula (II) have antibacterial activity: wherein Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH); $R_1$ represents hydrogen, methyl or trifluoromethyl, or, except when Z is a radical of formula -N(OH)CH(=0), a hydroxy, halo or amino group; $R_2$ represents a group $R_{10}$-$(V)_n$-$(ALK)_m$- wherein $R_{10}$ represents hydrogen, or an optionally substituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, cycloalkyl, aryl, or heterocyclyl group, ALK represents a straight or branched divalent $C_1$-$C_6$ alkylene, $C_2$ -$C_6$ alkenylene, or C2-C6 alkynylene radical, and may be interrupted by one or more non-adjacent -NH-, -O- or -S- linkages, V represents -NH-, -O- or-S-, m and n are independently 0 or 1; $R_3$ represents the side chain of a natural or non-natural alpha amino acid; $R_4$ represents hydrogen or $C_1$-$C_3$ alkyl; Y represents N or CH; ring A is optionally substituted on one or more ring carbon atoms by $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, or halo; and $R_5$ represents a group (IIA): wherein m is 0 or 1; $Alk^1$ represents a divalent $C_1$-$C_3$ alkylene radical; Z represents hydrogen or an optionally substituted cycloalkyl, phenyl or heterocyclic group.

WO 03/089412 A1

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/01541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D401/06 C07D409/06 C07D405/06 C07D417/14
C07D401/14 C07D413/06 C07D417/06 C07D513/04 A61K31/45
A61K31/4523 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | CHEMICAL ABSTRACTS, vol. 125, no. 1, 1 July 1996 (1996-07-01) Columbus, Ohio, US; abstract no. 11473, FUJISAWA PHARMACEUTICAL CO., LTD., JAPAN: "Preparation of N-(N-hydroxy-2-isobutyl-3-methyl-succinamy l)amino acid derivatives as collagenase inhibitors" XP002251429 abstract | 1 |
| A | & JP 08 053403 A (FUJISAWA PHARMACEUTICAL CO., LTD., JAPAN) 27 February 1996 (1996-02-27) --- -/-- | 14-17 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 August 2003 | 28/08/2003 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016 | Beslier, L |

# INTERNATIONAL SEARCH REPORT

Internati[redacted]Application No
PCT/GB 03/01541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 00 61134 A (BRITISH BIOTECH PHARMACEUTICALS LTD.) 19 October 2000 (2000-10-19) the whole document | 1-17 |
| A | WO 01 10835 A (BRITISH BIOTECH PHARMACEUTICALS LTD.) 15 February 2001 (2001-02-15) particularly examples 1 and 12 | 1-17 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 03/01541

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|---|
| JP 8053403 | A | 27-02-1996 | NONE | | |
| WO 0061134 | A | 19-10-2000 | AU | 3979200 A | 14-11-2000 |
| | | | EP | 1169031 A1 | 09-01-2002 |
| | | | WO | 0061134 A1 | 19-10-2000 |
| | | | JP | 2002541197 T | 03-12-2002 |
| WO 0110835 | A | 15-02-2001 | WO | 0110835 A1 | 15-02-2001 |
| | | | AU | 5296199 A | 05-03-2001 |
| | | | EP | 1210330 A1 | 05-06-2002 |

# PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ



I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Andrew Gersey

Dated 25 April 2003

Patents Form 1/77

Patents Act 1977
Rules 16

The Patent Office

THE PATENT OFFICE
K
13 APR 2002
NEWPORT

1/77

# Request for grant of a patent

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

| | | |
|---|---|---|
| 1. Your reference | 237/AJW | |
| 2. Patent application number | 0208579.3 | 15APR02 E711006-1 D03018<br>P01/7700 0.00-0208579.3<br>13 APR 2002 |
| 3. Full name, address and postcode of the or of each applicant | **British Biotech Pharmaceuticals Ltd**<br>**Watlington Road**<br>**Cowley**<br>**Oxford OX4 5LY** | |
| Patents ADP number | 8330623002 ~~9373001~~ | |
| If the applicant is a corporate body, give the country/state of its corporation | **GB** | |
| 4. Title of invention | **Antibacterial Agents** | |
| 5. Name of your agent | **Alan J. Walls** | |
| Address for service in the United Kingdom to which all correspondence should be sent | **British Biotech Pharmaceuticals Ltd**<br>**Watlington Road**<br>**Cowley**<br>**Oxford OX4 5LY** | |
| Patents ADP number | 8330623002 ~~17442004~~ | |

| | | | |
|---|---|---|---|
| 6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number | Country | Priority application no. | Date of filing *(day/month/year)* |
| 7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application | Number of earlier applications | | Date of filing *(day/month/year)* |
| 8. Is a statement of inventorship and of right to grant of a patent required in support of this request? | Yes | | |

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

| | |
|---|---|
| Continuation sheets of this form | 0 |
| Description | 29 |
| Claims(s) | 7 |
| Abstract | 0 |
| Drawing(s) | 0 |

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | 0 |
| Translations of priority documents | 0 |
| Statement of inventorship and right to grant a patent | 0 |
| Request for preliminary examination | 0 |
| Request for substantive examination | 0 |
| Any other documents | 0 |

11. I/We request the grant of a patent on the basis of this application.

Signature  Date **11 April 2002**

**Anthony Weir**
**Director**
**For and on behalf of British Biotech Pharmaceuticals Ltd**

12. Name and daytime telephone number of person to contact in the United Kingdom **Alan J. Walls**
**01865 748747**

# Antibacterial Agents

This invention relates to novel hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity, to methods of treatment using such compounds, and to pharmaceutical and veterinary compositions comprising such compounds.

## Background to the Invention

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes.

Amongst the Gram-positive pathogens, such as Staphylococci, Streptococci, Mycobacteria and Enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium.*

Pathogenic bacteria are often resistant to the aminoglycoside, β-lactam (penicillins and cephalosporins), and chloramphenicol types of antibiotic. This resistance involves the enzymatic inactivation of the antibiotic by hydrolysis or by formation of inactive derivatives. The β-lactam (penicillin and cephalosporin) family of antibiotics are characterised by the presence of a β-lactam ring structure. Resistance to this

family of antibiotics in clinical isolates is most commonly due to the production of a "penicillinase" (β-lactamase) enzyme by the resistant bacterium which hydrolyses the β-lactam ring thus eliminating its antibacterial activity.

Recently there has been an emergence of vancomycin-resistant strains of enterococci (Woodford N. 1998 Glycopeptide-resistant enterococci: a decade of experience. Journal of Medical Microbiology. 47(10):849-62). Vancomycin-resistant enterococci are particularly hazardous in that they are frequent causes of hospital based infections and are inherently resistant to most antibiotics. Vancomycin works by binding to the terminal D-Ala-D-Ala residues of the cell wall peptidioglycan precursor. The high-level resistance to vancomycin is known as VanA and is conferred by a genes located on a transposable element which alter the terminal residues to D-Ala-D-lac thus reducing the affinity for vancomycin.

In view of the rapid emergence of multidrug-resistant bacteria, the development of antibacterial agents with novel modes of action that are effective against the growing number of resistant bacteria, particularly the vancomycin resistant enterococci and β-lactam antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus,* is of utmost importance.

Brief Description of the Invention

This invention is based on the finding that certain hydroxamic acid and N-formyl hydroxylamine derivatives have antibacterial activity, and makes available a new group of antibacterial agents. It has been found that the compounds with which this invention is concerned are antibacterial with respect to a range of bacteria, with potency against Gram-positive organisms generally being greater than against Gram-negatives. Many of the compounds of the invention show activity against bacteria responsible for respratory infections, such as *Streptococcus pneumoniae* and *Haemophilus influenzae.*

Although it may be of interest to establish the mechanism of action of the

compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

All ribosome-mediated synthesis of proteins starts with a methionine residue. In prokaryotes the methionyl moiety carried by the initiator tRNA is N-formylated prior to its incorporation into a polypeptide. Consequently, N-formylmethionine is always present at the N-terminus of a nascent bacterial polypeptide. However, most mature proteins do not retain the N-formyl group or the terminal methionine residue. Deformylation is required prior to methionine removal, since methionine aminopeptidase does not recognise peptides with an N-terminal formylmethionine residue (Solbiati et al., J. Mol. Biol. 290:607-614, 1999). Deformylation is, therefore, a crucial step in bacterial protein biosynthesis and the enzyme responsible, PDF, is essential for normal bacterial growth. Although the gene encoding PDF (*def*) is present in all pathogenic bacteria for which sequences are known (Meinnel et al., J. Mol. Biol, 266:939-49, 1997), it has no eukaryotic counterpart, making it an attractive target for antibacterial chemotherapy.

The isolation and characterisation of PDF has been facilitated by an understanding of the importance of the metal ion in the active site (Groche et al., Biophys. Biochem. Res. Commun., 246:324-6, 1998). The $Fe^{2+}$ form is highly active *in vivo* but is unstable when isolated due to oxidative degradation (Rajagopalan et al., J. Biol. Chem. 273:22305-10, 1998). The $Ni^{2+}$ form of the enzyme has specific activity comparable with the ferrous enzyme but is oxygen-insensitive (Ragusa et al., J. Mol. Biol. 1998, 280:515-23, 1998). The $Zn^{2+}$ enzyme is also stable but is almost devoid of catalytic activity (Rajagopalan et al., J. Am. Chem. Soc. 119:12418-12419, 1997).

Several X-ray crystal structures and NMR structures of *E. coli* PDF, with or without bound inhibitors, have been published (Chan et al., Biochemistry 36:13904-9, 1997; Becker et al., Nature Struct. Biol. 5:1053-8, 1998; Becker et al., J. Biol. Chem.

273:11413-6, 1998; Hao et al., Biochemistry, 38:4712-9, 1999; Dardel et al., J. Mol. Biol. 280:501-13, 1998; O'Connell et al., J. Biomol. NMR, 13:311-24, 1999), indicating similarities in active site geometry to metalloproteinases such as thermolysin and the metzincins.

Recently the substrate specificity of PDF has been extensively studied (Ragusa et al., J. Mol. Biol. 289:1445-57, 1999; Hu et al., Biochemistry 38:643-50, 1999; Meinnel et al., Biochemistry, 38:4287-95, 1999). These authors conclude that an unbranched hydrophobic chain is preferred at P1', while a wide variety of P2' substituents are acceptable and an aromatic substituent may be advantageous at the P3' position. There have also been reports that small peptidic compounds containing an H-phosphonate (Hu et al., Bioorg. Med. Chem. Lett., 8:2479-82, 1998) or thiol (Meinnel et al., Biochemistry, 38:4287-95, 1999) metal binding group are micromolar inhibitors of PDF. Peptide aldehydes such as calpeptin (N-Cbz-Leu-norleucinal) have also been shown to inhibit PDF (Durand et al., Arch. Biochem. Biophys., 367:297-302, 1999). However, the identity of the metal binding group and its spacing from the rest of the molecule ("recognition fragment") has not been studied extensively. Furthermore, non-peptidic PDF inhibitors, which may be desirable from the point of view of bacterial cell wall permeability or oral bioavailability in the host species, have not been identified.

Related Prior Art

Certain N-formyl hydroxylamine derivatives have previously been claimed in the patent publications listed below, although very few examples of such compounds have been specifically made and described:

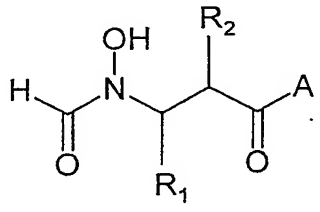
| | |
|---|---|
| EP-B-0236872 | (Roche) |
| WO 92/09563 | (Glycomed) |
| WO 92/04735 | (Syntex) |
| WO 95/19965 | (Glycomed) |
| WO 95/22966 | (Sanofi Winthrop) |

| | |
|---|---|
| WO 95/33709 | (Roche) |
| WO 96/23791 | (Syntex) |
| WO 96/16027 | (Syntex/Agouron) |
| WO 97/03783 | (British Biotech) |
| WO 97/18207 | (DuPont Merck) |
| WO 98/38179 | (GlaxoWellcome) |
| WO 98/47863 | (Labs Jaques Logeais) |

The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis.

In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives, however, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) discloses certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors.

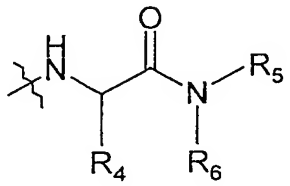
Our copending International Patent Application No. WO 99/39704 describes and claims, *inter alia*, the use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of an antibacterial composition:



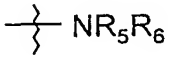

(I)

wherein $R_1$ represents hydrogen, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkyl substituted by one or more halogen atoms; $R_2$ represents a substituted or unsubstituted $C_1$-$C_6$ alkyl,

cycloalkyl($C_1$-$C_6$ alkyl)- or aryl($C_1$-$C_6$ alkyl)- group; and A represents a group of formula (IA), or (IB):



(IA)



(IB)

wherein $R_4$ represents the side chain of a natural or non-natural alpha amino acid, and $R_5$ and $R_6$ when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring.

Very many hydroxamic acid derivatives are known. Many have been disclosed as having matrix metalloproteinase (MMP) inhibitory activity, and thus to be potentially useful for the treatment of diseases mediated by MMPs, for example cancer, arthritides, and conditions involving tissue remodeling such as wound healing, and restenosis. In addition our International Patent Application No. WO 99/59568 describes the use of analogues of the N-formylhydroxylamine derivatives of WO 99/39704 (wherein the N-formylhydroxylamine group is replaced by a hydroxamic acid group) in the preparation of an antibacterial composition.

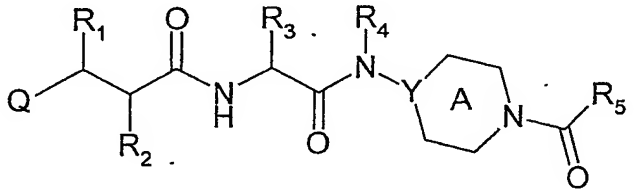
Brief Description of the Invention

This invention relates to a group of antibacterially active hydroxamic acid and and N-formyl hydroxylamine compounds which differ in structure from those of International Patent Applications Nos. WO 99/59568 and WO 99/39704, principally in the nature of the -$NR_5R_6$ group (see formulae (I), (IA) above and the hydroxamic acid analogues thereof). In those applications, $R_5$ may be $C_1$-$C_6$ alkyl and $R_6$ may be an optionally substituted heterocuclic ring. The term "optionally substituted" as used in relation to the saturated heterocyclic ring $R_6$ is defined as meaning certain specific

substituents. In the present compounds, the group R5 is also $C_1$-$C_6$ alkyl and R6 is also substituted heterocyclic ring, namely piperidinyl or piperaxinyl, but the substituents are different from those permitted by WO 99/59568 and WO 99/39704. The group $-NR_5R_6$ of the N-formyl hydroxylamines and hydroxamic acids of the invention is also believed to distinguish the present compounds from those known in the MMP, TNF, ACE, and enkephalinase inhibitor art.

Detailed description of the invention

The present invention provides a compound of formula (II), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof




(II)

wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

$R_1$ represents hydrogen, methyl or trifluoromethyl, or, except when Z is a radical of formula -N(OH)CH(=O), a hydroxy, halo or amino group;

$R_2$ represents a group $R_{10}$-$(V)_n$-$(ALK)_m$- wherein

$R_{10}$ represents hydrogen, or a $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, cycloalkyl, aryl, or heterocyclyl group, any of which may be unsubstituted or substituted by ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, hydroxy, mercapto, ($C_1$-$C_6$)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo, -COOH, $-CONH_2$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein $R^A$ and $R^B$ are independently a ($C_1$-$C_6$)alkyl group and

ALK represents a straight or branched divalent $C_1$-$C_6$ alkylene, $C_2$-$C_6$ alkenylene, or $C_2$-$C_6$ alkynylene radical, and may be interrupted by one or more non-adjacent -NH-, -O- or -S- linkages,

V represents -NH-, -O- or -S-, and

m and n are independently 0 or 1;

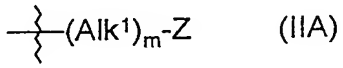
$R_3$ represents the side chain of a natural or non-natural alpha amino acid;

$R_4$ represents hydrogen or $C_1$-$C_3$ alkyl;

Y represents N or CH;

ring A is optionally substituted on one or more ring carbon atoms by $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, or halo; and

$R_5$ represents a group (IIA),



(IIA)

wherein

m is 0 or 1;

$Alk^1$ represents a divalent $C_1$-$C_3$ alkylene radical;

Z represents cycloalkyl, phenyl or monocyclic heterocyclic, which is optionally substituted by

$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, or $(C_2$-$C_6)$alkynyl,

phenyl, or halophenyl,

trifluoromethyl,

monocyclic 5 or 6-membered hetrocyclic,

benzyl, or halophenylmethyl,

hydroxy, phenoxy, ($C_1$-$C_6$)alkoxy, or hydroxy($C_1$-$C_6$)alkyl,

mercapto, ($C_1$-$C_6$)alkylthio or mercapto($C_1$-$C_6$)alkyl,

oxo,

nitro,

cyano (-CN)

halo (bromo, chloro, fluoro, or iodo)

-COOH, or -$COOR^A$,

-$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$

-$COR^A$, -$SO_2R^A$,

-$NHCOR^A$,

-$NH_2$, -$NHR^A$, or -$NR^AR^B$,

wherein $R^A$ and $R^B$ are independently a ($C_1$-$C_6$) alkyl group, or $R^A$ and $R^B$ taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by ($C_1C_3$)alkyl, hydroxy, or hydroxy($C_1$-$C_3$)alkyl.

In another aspect, the invention provides a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (II) as defined above.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound of formula (II) as defined above to the site of contamination.

The compounds of formula (II) as defined above may be used as component(s) of

antibacterial cleaning or disinfecting materials.

On the hypothesis that the compounds (II) act by inhibition of intracellular PDF, the most potent antibacterial effect may be achieved by using compounds which efficiently pass through the bacterial cell wall. Thus, compounds which are highly active as inhibitors of PDF in vitro and which penetrate bacterial cells are preferred for use in accordance with the invention. It is to be expected that the antibacterial potency of compounds which are potent inhibitors of the PDF enzyme in vitro, but are poorly cell penetrant, may be improved by their use in the form of a prodrug, ie a structurally modified analogue which is converted to the parent molecule of formula (II), for example by enzymic action, after it has passed through the bacterial cell wall.

As used herein the term "($C_1$-$C_6$)alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent ($C_1$-$C_3$)alkylene radical" means a saturated hydrocarbon chain having from 1 to 3 carbon atoms and two unsatisfied valencies.

As used herein the term "($C_2$-$C_6$)alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "$C_2$-$C_6$ alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from

3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring containing one or more heteroatoms;. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a 5-7 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, including for example, pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzofuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, maleimido and succinimido groups.

As used herein the terms "side chain of a natural alpha-amino acid" and "side chain of a non-natural alpha-amino acid" mean the group $R^x$ in respectively a natural and non-natural amino acid of formula $NH_2$-CH($R^x$)-COOH.

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α-aminoadipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine, ornithine, pipecolic acid, and thyroxine.

In natural alpha-amino acid side chains which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl

groups as in arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine, such functional substituents may optionally be protected.

Likewise, in the side chains of non-natural alpha amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups, such functional substituents may optionally be protected.

The term "protected" when used in relation to a functional substituent in a side chain of a natural or non-natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. The widely used handbook by T. W. Greene and P. G. Wuts "Protective Groups in Organic Synthesis" Second Edition, Wiley, New York, 1991 reviews the subject. For example, carboxyl groups may be esterified (for example as a $C_1$-$C_6$ alkyl ester), amino groups may be converted to amides (for example as a $NHCOC_1$-$C_6$ alkyl amide) or carbamates (for example as an $NHC(=O)OC_1$-$C_6$ alkyl or $NHC(=O)OCH_2Ph$ carbamate), hydroxyl groups may be converted to ethers (for example an $OC_1$-$C_6$ alkyl or a $O(C_1$-$C_6$ alkyl)phenyl ether) or esters (for example a $OC(=O)C_1$-$C_6$ alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a $SC(=O)C_1$-$C_6$ alkyl thioester).

There are several actual or potential chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereoconfiguration of the carbon atom carrying the $R_2$ group is R; that of the carbon atom carrying the $R_4$ group (when asymmetric) is S; and that of the carbon atom carrying the $R_1$ group (when asymmetric) is R.

In the compounds of the invention:

When Q is a radical of formula -N(OH)CH(=O), $R_1$ may be, for example, hydrogen, methyl, or trifuoromethyl. Hydrogen is currently preferred.

When Q is is a radical of formula -C(=O)NH(OH), $R_1$ may be, for example, hydrogen, methyl, trifluoromethyl, hydroxy, halo or amino. Again hydrogen is currently preferred.

$R_2$ may be, for example:

optionally substituted $C_1$-$C_8$ alkyl, $C_3$-$C_6$ alkenyl, $C_3$-$C_6$ alkynyl or cycloalkyl;

phenyl($C_1$-$C_6$ alkyl)-, phenyl($C_3$-$C_6$ alkenyl)- or phenyl($C_3$-$C_6$ alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl($C_1$-$C_6$ alkyl)- for example cycloalkylmethyl, cycloalkyl($C_3$-$C_6$ alkenyl)- or cycloalkyl($C_3$-$C_6$ alkynyl)-, optionally substituted in the cycloalkyl ring;

heterocyclyl($C_1$-$C_6$ alkyl)-, heterocyclyl($C_3$-$C_6$ alkenyl)- or heterocyclyl($C_3$-$C_6$ alkynyl)- optionally substituted in the heterocyclyl ring; or

($C_1$-$C_3$)alkyl-S-($C_1$-$C_3$)alkyl-, or ($C_1$-$C_3$)alkyl-O-($C_1$-$C_3$)alkyl-.

Specific examples of $R_2$ groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-acetyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl,

cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at $R_2$ are $(C_1$-$C_6)$alkyl-, cycloalkylmethyl-, $(C_1$-$C_3)$alkyl-S-$(C_1$-$C_3)$alkyl-, or $(C_1$-$C_3)$alkyl-O-$(C_1$-$C_3)$alkyl-, especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

$R_3$ may be, for example

the characterising group of a natural α amino acid, for example benzyl, or 4-methoxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group $-[Alk]_nR_9$ where Alk is a $(C_1$-$C_6)$alkylene or $(C_2$-$C_6)$alkenylene group optionally interrupted by one or more -O-, or -S- atoms or $-N(R_{12})$- groups [where $R_{12}$ is a hydrogen atom or a $(C_1$-$C_6)$alkyl group], n is 0 or 1, and $R_9$ is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) $R_9$ may additionally be hydroxy, mercapto, $(C_1$-$C_6)$alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein $R^A$ and $R^B$ are independently a $(C_1$-$C_6)$alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula $-OCH_2COR_8$ where $R_8$ is hydroxyl, amino, $(C_1$-$C_6)$alkoxy, phenyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino, di$((C_1$-$C_6)$alkyl)amino, phenyl$(C_1$-$C_6)$alkylamino; or

a heterocyclic($C_1$-$C_6$)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, ($C_1$-$C_6$)alkoxy, cyano, ($C_1$-$C_6$)alkanoyl, trifluoromethyl ($C_1$-$C_6$)alkyl, hydroxy, formyl, amino, ($C_1$-$C_6$)alkylamino, di-($C_1$-$C_6$)alkylamino, mercapto, ($C_1$-$C_6$)alkylthio, hydroxy($C_1$-$C_6$)alkyl, mercapto($C_1$-$C_6$)alkyl or ($C_1$-$C_6$)alkylphenylmethyl; or

a group $-CR_aR_bR_c$ in which:

each of $R_a$, $R_b$ and $R_c$ is independently hydrogen, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, phenyl($C_1$-$C_6$)alkyl, ($C_3$-$C_8$)cycloalkyl; or

$R_c$ is hydrogen and $R_a$ and $R_b$ are independently phenyl or heteroaryl such as pyridyl; or

$R_c$ is hydrogen, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, phenyl($C_1$-$C_6$)alkyl, or ($C_3$-$C_8$)cycloalkyl, and $R_a$ and $R_b$ together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

$R_a$, $R_b$ and $R_c$ together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

$R_a$ and $R_b$ are each independently ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, phenyl($C_1$-$C_6$)alkyl, or a group as defined for $R_c$ below other than hydrogen, or $R_a$ and $R_b$ together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and $R_c$ is hydrogen, -OH, -SH, halogen, -CN, $-CO_2H$, ($C_1$-$C_4$)perfluoroalkyl, $-CH_2OH$, $-CO_2$($C_1$-$C_6$)alkyl, -O($C_1$-$C_6$)alkyl, -O($C_2$-$C_6$)alkenyl, -S($C_1$-$C_6$)alkyl, -SO($C_1$-$C_6$)alkyl, $-SO_2$($C_1$-$C_6$) alkyl, -S($C_2$-$C_6$)alkenyl, -SO($C_2$-$C_6$)alkenyl, $-SO_2$($C_2$-$C_6$)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or $-SO_2$- and W represents a phenyl, phenylalkyl, ($C_3$-$C_8$)cycloalkyl, ($C_3$-$C_8$)cycloalkylalkyl, ($C_4$-

$C_8$)cycloalkenyl, ($C_4$-$C_8$)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -$CO_2H$, -$CO_2$($C_1$-$C_6$)alkyl, -$CONH_2$, -CONH($C_1$-$C_6$)alkyl, -CONH($C_1$-$C_6$alkyl)$_2$, -CHO, -$CH_2OH$, ($C_1$-$C_4$)perfluoroalkyl, -O($C_1$-$C_6$)alkyl, -S($C_1$-$C_6$)alkyl, -SO($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$NO_2$, -$NH_2$, -NH($C_1$-$C_6$)alkyl, -N(($C_1$-$C_6$)alkyl)$_2$, -NHCO($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_4$-$C_8$)cycloalkenyl, phenyl or benzyl.

Examples of particular $R_3$ groups include methyl, ethyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxethyl, 2-carboxyethyl, 2-methylcarbamoylethyl, 2-carbamoylethyl, and 4-aminobutyl. Presently preferred $R_3$ groups include tert-butyl, iso-butyl, benzyl, isopropyl and methyl.

$R_4$ may be, for example methyl or ethyl. Methyl is currently preferred.

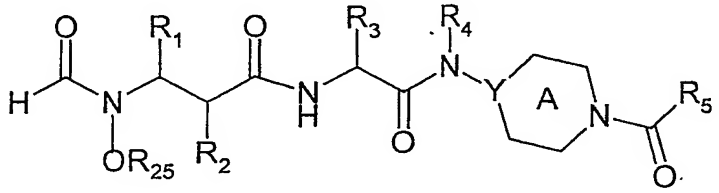
When m is 1, $Alk^1$ may be, for example, -($CH_2$)- or -($CH_2CH_2$)-.

Z may be, for example, a cyclopentyl, cyclohexyl, phenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2-or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring any of which may optionally be substituted by, for example, hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, methyl, ethyl, trfluoromethyl, fluoro, chloro, amino, methylamino, or dimethylamino.

Specific examples of substituents (IIA) include those present in the compounds specifically named, and/or exemplified herein.

Examples of specific compounds of the invention are those of the Examples herein. In those Examples, where a compound of formula (II) above wherein Q is an N-formylhydroxylamine radical -N(OH)CH(=O) is disclosed, it is to be understood that the equivalent compound wherein Q is a hydroxamate radical -C(=O)NH(OH) is also a specific compound of the invention, and *vice versa*.

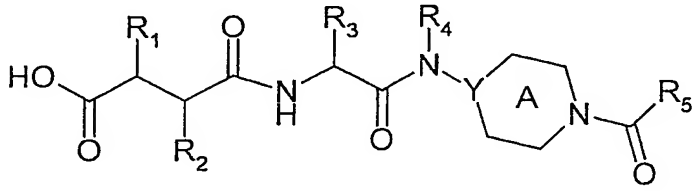
Compounds of the invention in which Q is an N-formylhydroxyamino group may be prepared by deprotecting an O-protected N-formyl-N-hydroxyamino compound of formula (III):




(III)

in which $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and Y are as defined in general formula (II) and $R_{25}$ is a hydroxy protecting group removable to leave a hydroxy group by hydrogenolysis or hydrolysis. Benzyl is a preferred $R_{25}$ group for removal by hydrogenolysis, and tert-butyl and tetrahydropyranyl are preferred groups for removal by acid hydrolysis.

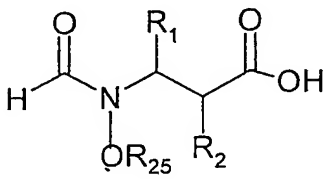
Compounds of the invention in which Q is a hydroxamic acid group may be prepared by reacting the parent compound wherein Q is a carboxylic acid group (IIIA)



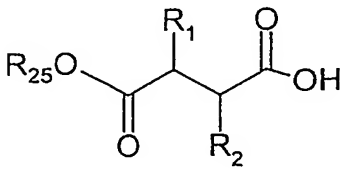

(IIIA)

with hydroxylamine or an N- and/or O-protected hydroxylamine, and thereafter removing any O- or N-protecting groups

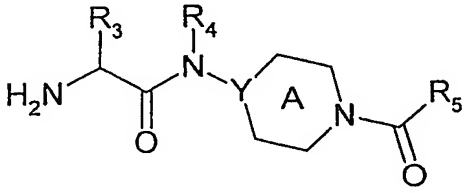
Compounds of formula (III) or (IIIA) may be prepared by causing an acid of formula (IV) or (IVA) or an activated derivative thereof to react with an amine of formula (V)



(IV)



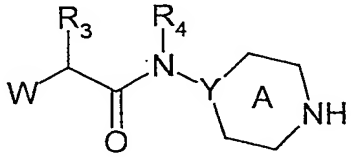
(IVA)



(V)

wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and Y are as defined in general formula (II) except that any substituents in $R_1$ $R_2$, $R_4$, and $R_5$which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and $R_{25}$ is as defined in relation to formula (III) above, and optionally removing protecting groups $R_1$, $R_2$, $R_4$, and $R_5$.

Compounds of formula (V) may be prepared by N-acylation of a compound of formula (VI) with, for example, the acid chloride $R_5COCl$



(VI)

wherein $R_4$, $R_5$ and Y are as defined in general formula (V), and W is a protected amino group, and then removing the amino protecting group(s).

Compounds (II) of the invention may also be prepared by N-acylation of the corresponding piperazine or piperidine parent compound, as in the Examples herein.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases,

for example sodium, potassium, magnesium, and calcium salts.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body

weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples illustrate embodiments of the invention. In the Examples, the following abbreviations have been used throughout:

| | |
|---|---|
| DCM | Dichloromethane |
| DIEA | Diisopropylethylamine |
| DMF | Dimethylformamide |
| HATU | O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HOBt | 1-Hydroxy-7-benzotriazole |
| HPLC | High performance liquid chromatography |
| LRMS | Low resolution mass spectrometry |
| NMR | Nuclear Magnetic Resonance |
| PyAOP7 | Azabenzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate |
| rt | Room temperature |
| RT | Retention time |
| TBTU | 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluorophosphate |
| TFA | Trifluoroacetic acid |

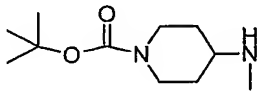
$^{1}H$ and $^{13}C$ spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 MHz (62.5 MHz for the $^{13}C$). Chemical shift values are expressed in δ (ppm) and abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, b = broad and app = apparent. Mass spectra were obtained using a Perkin Elmer Sciex API 165. Analytical HPLC was run on a Beckman System Gold, using Waters Symmetry C18 column (50 mm, 4.6 mm) with 20 to 90% solvent B gradient (1.5 ml/min) as the mobile phase. [Solvent A: 0.05%

TFA in 10% MeCN 90% water, Solvent B: 0.05% TFA in 10% water 90% MeCN, 5 min gradient time], detection wavelength at 220 or 214 nm. Preparative HPLC was run on a Gilson autoprep instrument using a C18 Waters delta pak (15µm, 300 Å, 25 mm, 100 mm) with 10 to 90% solvent B gradient as the mobile phase at a flow rate of 15 ml/min. [Solvent A 10% MeCN/water; Solvent B: 10% water/MeCN, 8 min gradient time], UV detection was at 220 or 214 nm.

**Preparation of 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)propionylamino]-3,3,*N*-trimethyl-*N*-piperidin-4-yl-butyramide (Intermediate 1)**

Step 1

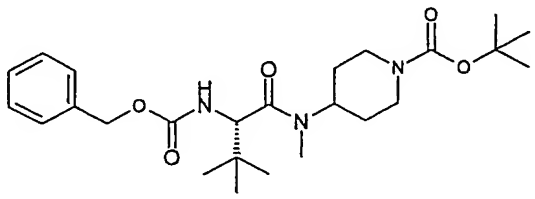
**4-Methylamino-piperidine-1-carboxylic acid *tert*-butyl ester**



To a solution of *tert*-butoxy-piperidone (10 g, 50 mmol) in EtOH (100 ml) was added N-methylamine (10 ml of a 33% solution in EtOH) and palladium on carbon (1 g, 10% w/w), hydrogen was bubbled through the reaction mixture for 2 h. The mixture was stirred under a blanket of hydrogen for 18 h at RT. The Pd/C was filtered off and the solvent removed *in vacuo* to yield the title compound as a clear oil. LRMS: +ve ion 215 (M+1, 20%), 237 (M+Na, 15%). $^1$H-NMR (250MHz), δ ($CDCl_3$) 4.05 (2H, m), 2.80 (2H, m), 2.51 (1H, m), 2.45 (3H, s), 1.87 (2H, m), 1.62 (1H, s), 1.45 (9H, s), 1.25 (2H, m).

Step 2

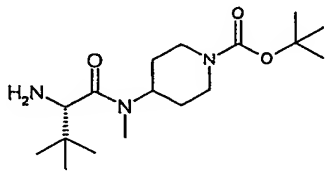
**4-[(2-Benzyloxycarbonylamino-3,3-dimethyl-butyryl-methyl-amino]-piperidine-1-carboxylic acid *tert*-butyl ester**



To a solution of Cbz-protected *tert*-leucine (500 mg, 1.9 mmol) in dichloromethane (10 ml) was added PyAOP (1.08 g, 2.1 mmol), HOAt (26 mg, 0.19 mmol), triethylamine and 4-Methylamino-piperidine-1-carboxylic acid *tert*-butyl ester (606 mg, 2.8 mmol). The reaction mixture was stirred for 18 h at Rt. The solvent was removed *in vacuo* and the yellow residue was redissolved in dichloromethane (80 ml) and was washed with 1M hydrochloric acid (2 x 80 ml), 1M sodium carbonate (2 x 80 ml), brine (1 x 80 ml) and dried over anhydrous magnesium sulphate to yield a clear oil (2 g). Flash chromatography (2% MeOH, dichloromethane) yielded the title compound as a white foam (870 mg, 100%) which contained a slight impurity. HPLC. 6.9 min (85%); LRMS: +ve ion 462 (M+1, 5%), 484 (M+Na, 20%). The compound was progressed to the next step without any further purification.

Step 3

**4-[(2-Amino-3,3-dimethyl-butyryl)-methyl-amino]-piperidine-1-carboxylic acid *tert*-butyl ester**

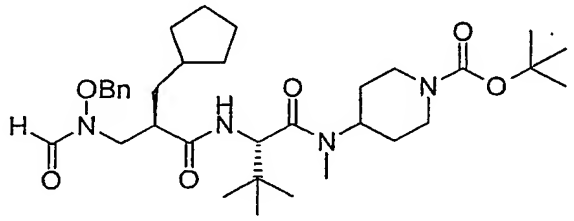


To a solution of 4-[(2-Benzyloxycarbonylamino-3,3-dimethyl-butyryl-methyl-amino]-

piperidine-1-carboxylic acid *tert*-butyl ester (500 mg, 1.1 mmol) in EtOH (10 ml) was added palladium on carbon (50 mg, 10% w/w), hydrogen was bubbled through the reaction mixture for 2 h. The mixture was stirred under a blanket of hydrogen for 18 h at Rt. The Pd/C was filtered off and the solvent removed *in vacuo* to yield the title compound as a yellow oil which was progressed to the next step without further purification. LRMS: +ve ion 328 (M+1, 100%).

Step 4

**4-({2-[3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-methyl-amino)-piperidine-1-carboxylic acid *tert*-butyl ester**

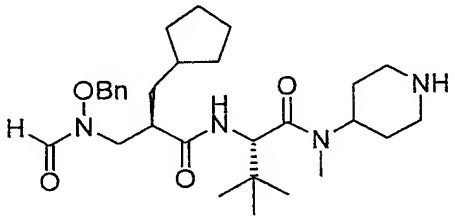


To a solution of of 3-(Benzyloxy-formyl-amino)-2*R*-cyclopentylmethyl-propionic acid (288 mg, 0.94 mmol) in dichloromethane/DMF, (4:1, 25 ml) was added WSC (198 mg, 1.04 mmol), HOAt (13 mg, 94.5 μmol), triethylamine (196 μl, 1.4 mmol) and 4-[(2-Amino-3,3-dimethyl-butyryl)-methyl-amino]-piperidine-1-carboxylic acid *tert*-butyl ester (340 mg, 1.04 mmol) at Rt. The reaction mixture was stirred for 18 h at Rt and the solvent was removed *in vacuo* to yield a yellow oil which was redissolved in dichloromethane (70 ml) and was washed with 1M hydrochloric acid (1 x 50 ml), 1M sodium carbonate (1 x 50 ml), brine (1 x 50 ml) and was dried over anhydrous magnesium sulphate. The solvent was removed under vacuum to yield a clear oil (517 mg). Flash chromatography gradient 2:1 to 1:1 hexane/ethyl acetate yielded the title compound as a white foam (300 mg, 52%). . HPLC. 7.1 min (85%); LRMS:

+ve ion 462 (M+1, 5%), 484 (M+Na, 20%)

Step 5

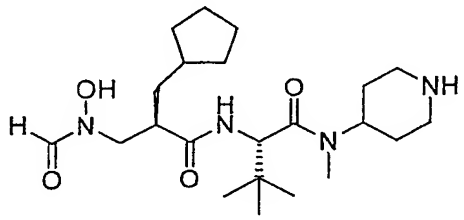
**2-[3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionylamino]-3,3,*N*-trimethyl-*N*-piperidin-4-yl-butyramide**




To a solution of 4-({2-[3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionylamino]-3,3-dimethyl-butyryl}-methyl-amino)-piperidine-1-carboxylic acid *tert*-butyl ester in dichloromethane (5 ml) was added acetic acid (1 ml) and then boron trifluoride etherate (91 µl, 0.71 mmol) at 0 °C. The reaction mixture was stirred at 0 C for 1.25 h, more dichloromthane was added (15 ml) and the organic layer was then washed with 1M sodium carbonate (1 x 30 ml), dried over anhydrous magnesium sulphate and the solvent was removed *in vacuo* to yield the title compound as a clear oil (98 mg, 78%). HPLC. 5.2 min (70%), salt formation due to secondary nitrogen is likely hence the purity; LRMS: +ve ion 515 (M+1, 100%). $^1$H-NMR (250MHz), δ ($CDCl_3$) 8.14 (0.6 H, brs, 8.14), 7.87 (0.4H, brs, 7.87), 7.37-7.26 (5H, m), 6.29 (0.4H, d, J 9.4 Hz), 6.25 (0.6H, d, J 9.4 Hz), 5.01-4.71(3H, m), 4.55-4.48 (1H, m), 3.8 (2H, brm), 3.20-3.10 (3H, m), 2.99 (2H, s), 2.81 (1H, s), 2.74-2.63 (2H, m), 2.60-2.55 (1H, m), 1.81-1.37 (13H, m), 1.07-0.97 (2H, m), 0.95-0.92 (11H, m).

**Step 5**

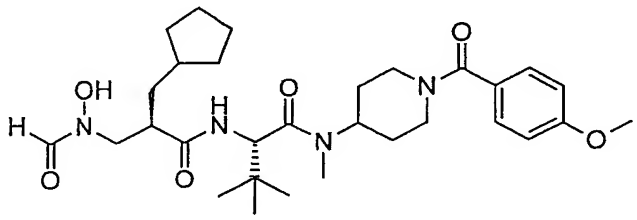
**2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)propionylamino]-3,3,*N*-trimethyl-*N*-piperidin-4-yl-butyramide (Intermediate 1)**



To a solution of 2-[3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionylamino]-3,3,*N*-trimethyl-*N*-piperidin-4-yl-butyramide (135 mg, 0.26 mmol) in EtOH (5 ml) was added Pd/C (14 mg, 15% w/w), hydrogen was bubbled through the suspensioin for 2 h and the reaction was then stirred for 18 h at Rt under a blanket of hydrogen. The catalyst was filtered off and the solvent was removed *in vacuo* to yield the title compound as a white solid (98 mg, 88%). ; LRMS: +ve ion 425 (M+1, 100%), -ve ion 423 (M-1, 100%). The NMR was complex due to the presence of rotamers and a zwitterion.

**Example 1**

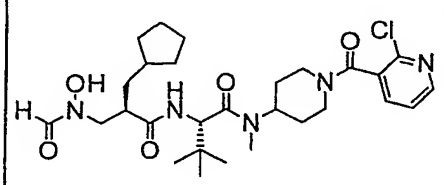
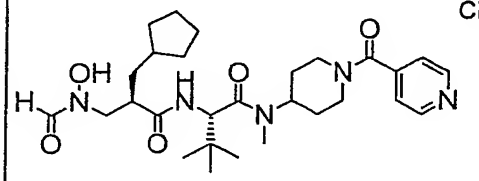
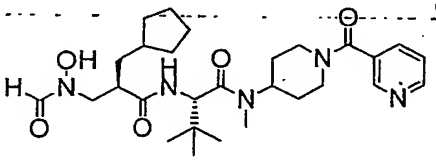
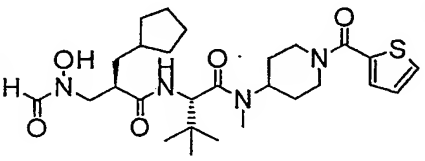
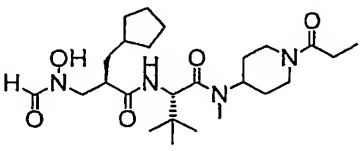
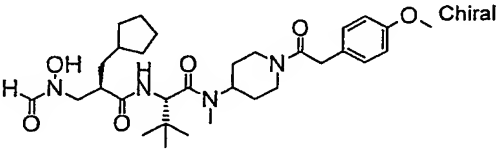
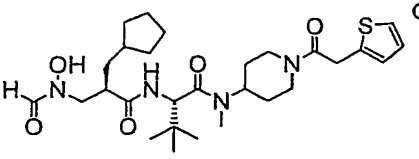
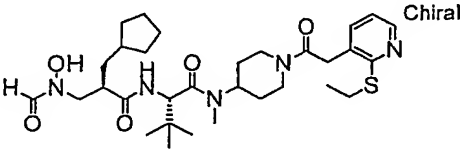
**2-[2-Cyclopentyl-3-(formyl-hydroxy-amino)-propionylamino]-*N*-[1-(4-methoxy-benzoyl)-piperidin-4-yl]-3,3,*N*-trimethyl-butyramide**

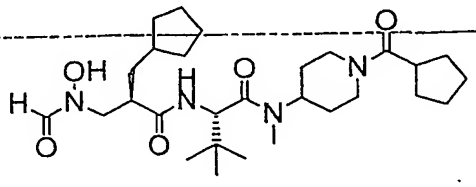
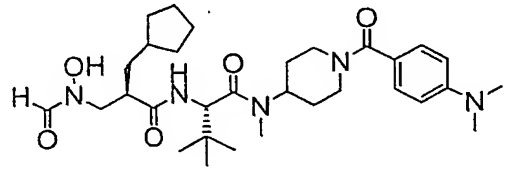
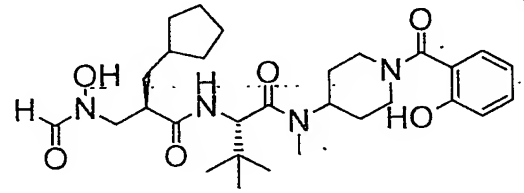


To a solution of 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)propionylamino]-

3,3,*N*-trimethyl-*N*-piperidin-4-yl-butyramide (Intermediate 1) ( 150 mg, 0.4 mmol) in dichloromethane (5 ml) was added 4-methoxy-benzoyl chloride (90.5 mg, 0.5 mmol) and triethylamine (73.4 µl, 0.5 mmol). The reaction mixture was stirred at RT for 18h. Aminomethyl polystyrene resin (0.89 mmol/g, 3 eq excess) was added and the reaction mixture was left to stir for a further 18 h. The resin was filtered off and the solvent was removed *in vacuo*, to yield the crude product. The title compound was purified by preparative HPLC to yield a white solid. HPLC: RT: 5.1 min (82% @ 214nm); ESMS: +ve: 559 (M+1, 20%);
-ve: 557 (M-1, 40%).

Compounds of Examples 2-12 were prepared in a manner analogous to that of Example 1. All compounds were purified by preparative HPLC

| Compound No. | Structure | Analytical Data |
|---|---|---|
| 2 |  Chiral | HPLC : RT: 4.7 min (81% @ 214nm)<br><br>ESMS: +ve: 564 (M+1, 30%); -ve: 563 (M-1, 10%) |
| 3 |  Chiral | HPLC: RT: 1.8 min (89% @ 214 nm)<br><br>ESMS:+ve: 530 (M+1, 60%), 552 (M+Na, 5%); -ve 528 (M-1, 10%) |
| 4 |  Chiral | HPLC: RT: 2.0 min (85% @ 214 nm)<br><br>ESMS: +ve: 530 (M+1, 100%); -ve: 528 (M-1, 20%) |
| 5 |  Chiral | RT: 5.1 min (80% @ 214 nm)<br><br>ESMS: +ve: 535 (M+1, 5%); -ve: 533(M-1, 30%) |
| 6 |  Chiral | HPLC: RT: 4.8 min (76%) @ 214 nm<br><br>ESMS: +ve: 481(M+1), 503 (M+Na); -ve: 479 (M-1) |
| 7 |  Chiral | HPLC: RT: 5.3 min (100%)<br><br>ESMS: +ve: 573(M+1), 595 (M+Na); -ve: 571 (M-1) |
| 8 |  Chiral | HPLC: RT: 5.2 min (100%) @ 214 nm<br><br>ESMS: +ve: 549 (M+1), 571 (M+Na); -ve: 547 (M-1) |
| 9 |  Chiral | HPLC: RT: 5.3 min (99%) @ 214 nm<br><br>ESMS: +ve: 590 (M+1), 612 (M+Na); -ve: 588 (M-1) |

| | | |
|---|---|---|
| 10 | Chiral  | HPLC: RT: 5.3 min (100%) @ 214 nm<br><br>ESMS: +ve: 521 (M+1), 543 (M+Na); -ve: 519 (M-1) |
| 11 | Chiral  | HPLC: RT: 4.8 min (100%) @ 214 nm<br><br>ESMS: +ve: 572 (M+1), 594 (M+Na) |
| 12 | Chiral  | HPLC: RT: 5.2 min (92%) @214 nm<br><br>ESMS: +ve: 567 (M+Na), 545 (M+1); - ve: 543 (M-1) |

Compound 2: *N*-[1-(2-Chloro-pyridine-3-carbonyl)-piperidin-4-yl]-2-[2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3,*N*-trimethyl-butyramide

Compound 3: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3,*N*-trimethyl-*N*-[1-(pyridine-4-carbonyl)-piperidin-4-yl]-butyramide

Compound 4: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3,*N*-trimethyl-*N*-[1-(pyridine-3-carbonyl)-piperidin-4-yl]-butyramide

Compound 5: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3,*N*-trimethyl-*N*-[1-(thiophene-2-carbonyl)-piperidin-4-yl]-butyramide

Compound 6: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3,*N*-trimethyl-*N*-[1-propionyl-piperidin-4-yl]-butyramide

Compound 7: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-*N*-{1-[2-(4-methoxy-phenyl)-acetyl]-piperidin-4-yl}-3,3,*N*-trimethyl-butyramide

Compound 8: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3,*N*-trimethyl-*N*-[1-(2-thiophen-2-yl-acetyl)-piperidin-4-yl]-butyramide

Compound 9: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-*N*-{1-[2-(2-ehtylsulfanyl-pyridin-3-yl)acetyl]-piperidin-4-yl}-3,3,*N*-trimethyl-butyramide

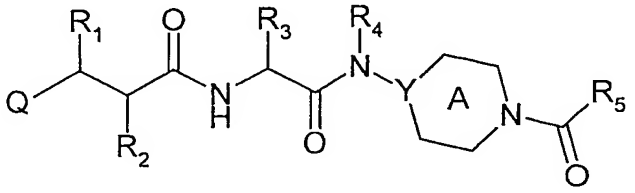
Compound 10: *N*-(1-Cyclopentanecarbonyl-piperidin-4-yl)-2[2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3,*N*-trimethyl-butyramide

Compound 11: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-*N*-[1-(4-dimethylamino-benzoyl)-piperidin-4-yl]-3,3,*N*-trimethyl-butyramide

Compound 12: 2-[2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-*N*-[1-(2-hydroxy-benzoyl)-piperidin-4-yl]-3,3, *N*-trimethyl-butyramide

Claims:

1. A compound of formula (II), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof




(II)

wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

$R_1$ represents hydrogen, methyl or trifluoromethyl, or, except when Z is a radical of formula -N(OH)CH(=O), a hydroxy, halo or amino group;

$R_2$ represents a group $R_{10}$-$(V)_n$-$(ALK)_m$- wherein

$R_{10}$ represents hydrogen, or a $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, cycloalkyl, aryl, or heterocyclyl group, any of which may be unsubstituted or substituted by ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, hydroxy, mercapto, ($C_1$-$C_6$)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo, -COOH, -$CONH_2$, -$COOR^A$, -$NHCOR^A$, -$CONHR^A$, -$NHR^A$, -$NR^AR^B$, or -$CONR^AR^B$ wherein $R^A$ and $R^B$ are independently a ($C_1$-$C_6$)alkyl group and

ALK represents a straight or branched divalent $C_1$-$C_6$ alkylene, $C_2$-$C_6$ alkenylene, or $C_2$-$C_6$ alkynylene radical, and may be interrupted by one or more non-adjacent -NH-, -O- or -S- linkages,

V represents -NH-, -O- or -S-, and

m and n are independently 0 or 1;

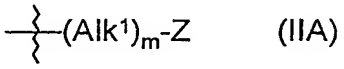
$R_3$ represents the side chain of a natural or non-natural alpha amino acid;

$R_4$ represents hydrogen or $C_1$-$C_3$ alkyl;

Y represents N or CH;

ring A is optionally substituted on one or more ring carbon atoms by $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, or halo; and

$R_5$ represents a group (IIA),



(IIA)

wherein

m is 0 or 1;

$Alk^1$ represents a divalent $C_1$-$C_3$ alkylene radical;

Z represents cycloalkyl, phenyl or monocyclic heterocyclic, which is optionally substituted by

$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, or $(C_2$-$C_6)$alkynyl,
phenyl, or halophenyl,
trifluoromethyl,
monocyclic 5 or 6-membered hetrocyclic,
benzyl, or halophenylmethyl,
hydroxy, phenoxy, $(C_1$-$C_6)$alkoxy, or hydroxy$(C_1$-$C_6)$alkyl,
mercapto, $(C_1$-$C_6)$alkylthio or mercapto$(C_1$-$C_6)$alkyl,
oxo,
nitro,

cyano (-CN)

halo (bromo, chloro, fluoro, or iodo)

-COOH, or -$COOR^A$,

-$CONH_2$, -$CONHR^A$, or -$CONR^AR^B$

-$COR^A$, -$SO_2R^A$,

-$NHCOR^A$,

-$NH_2$, -$NHR^A$, or -$NR^AR^B$,

wherein $R^A$ and $R^B$ are independently a ($C_1$-$C_6$) alkyl group, or $R^A$ and $R^B$ taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by ($C_1C_3$)alkyl, hydroxy, or hydroxy($C_1$-$C_3$)alkyl.

2. A method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound as claimed in claim 1.

3. A method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound as claimed in claim 1 to the site of contamination.

4. The use of a compound as claimed in claim 1 in the manufacture of an antibacterial composition.

5. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 together with a pharmaceutically of veterinarily acceptable carrier.

6. A compound as claimed in claim 1, a method as claimed in claim 2 or claim 3, the use as claimed in claim 4 or a composition as claimed in claim 5 wherein $R_1$ is

hydrogen.

7. A compound, method, use or composition as claimed in claim 6 wherein $R_2$ is $(C_1\text{-}C_6)$alkyl-, cycloalkyl$(C_1\text{-}C_6)$alkyl-, $(C_1\text{-}C_3)$alkyl-S-$(C_1\text{-}C_3)$alkyl-, or $(C_1\text{-}C_3)$alkyl-O-$(C_1\text{-}C_3)$alkyl-.

8. A compound, method, use or composition as claimed in claim 6 wherein $R_2$ is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

9. A compound, method, use or composition as claimed in any of the preceding claims wherein $R_3$ is

the characterising group of a natural α amino acid, for example benzyl, or 4-methoxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group $-[Alk]_nR_9$ where Alk is a $(C_1\text{-}C_6)$alkylene or $(C_2\text{-}C_6)$alkenylene group optionally interrupted by one or more -O-, or -S- atoms or $-N(R_{12})$- groups [where $R_{12}$ is a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group], n is 0 or 1, and $R_9$ is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) $R_9$ may additionally be hydroxy, mercapto, $(C_1\text{-}C_6)$alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, $-CONH_2$, $-COOR^A$, $-NHCOR^A$, $-CONHR^A$, $-NHR^A$, $-NR^AR^B$, or $-CONR^AR^B$ wherein $R^A$ and $R^B$ are independently a $(C_1\text{-}C_6)$alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula $-OCH_2COR_8$ where $R_8$ is hydroxyl, amino, $(C_1\text{-}C_6)$alkoxy, phenyl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylamino, di$((C_1\text{-}C_6)$alkyl)amino, phenyl$(C_1\text{-}C_6)$alkylamino; or

a heterocyclic($C_1$-$C_6$)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, ($C_1$-$C_6$)alkoxy, cyano, ($C_1$-$C_6$)alkanoyl, trifluoromethyl ($C_1$-$C_6$)alkyl, hydroxy, formyl, amino, ($C_1$-$C_6$)alkylamino, di-($C_1$-$C_6$)alkylamino, mercapto, ($C_1$-$C_6$)alkylthio, hydroxy($C_1$-$C_6$)alkyl, mercapto($C_1$-$C_6$)alkyl or ($C_1$-$C_6$)alkylphenylmethyl; or

a group $-CR_aR_bR_c$ in which:

each of $R_a$, $R_b$ and $R_c$ is independently hydrogen, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, phenyl($C_1$-$C_6$)alkyl, ($C_3$-$C_8$)cycloalkyl; or

$R_c$ is hydrogen and $R_a$ and $R_b$ are independently phenyl or heteroaryl such as pyridyl; or

$R_c$ is hydrogen, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, phenyl($C_1$-$C_6$)alkyl, or ($C_3$-$C_8$)cycloalkyl, and $R_a$ and $R_b$ together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

$R_a$, $R_b$ and $R_c$ together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

$R_a$ and $R_b$ are each independently ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, phenyl($C_1$-$C_6$)alkyl, or a group as defined for $R_c$ below other than hydrogen, or $R_a$ and $R_b$ together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and $R_c$ is hydrogen, -OH, -SH, halogen, -CN, $-CO_2H$, ($C_1$-$C_4$)perfluoroalkyl, $-CH_2OH$, $-CO_2$($C_1$-$C_6$)alkyl, -O($C_1$-$C_6$)alkyl, -O($C_2$-$C_6$)alkenyl, -S($C_1$-$C_6$)alkyl, -SO($C_1$-$C_6$)alkyl, $-SO_2$($C_1$-$C_6$) alkyl, -S($C_2$-$C_6$)alkenyl, -SO($C_2$-$C_6$)alkenyl, $-SO_2$($C_2$-$C_6$)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or $-SO_2$- and W represents a phenyl, phenylalkyl, ($C_3$-$C_8$)cycloalkyl, ($C_3$-$C_8$)cycloalkylalkyl, ($C_4$-

$C_8$)cycloalkenyl, ($C_4$-$C_8$)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -$CO_2$H, -$CO_2$($C_1$-$C_6$)alkyl, -$CONH_2$, -CONH($C_1$-$C_6$)alkyl, -CONH($C_1$-$C_6$alkyl)$_2$, -CHO, -$CH_2$OH, ($C_1$-$C_4$)perfluoroalkyl, -O($C_1$-$C_6$)alkyl, -S($C_1$-$C_6$)alkyl, -SO($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$NO_2$, -$NH_2$, -NH($C_1$-$C_6$)alkyl, -N(($C_1$-$C_6$)alkyl)$_2$, -NHCO($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_4$-$C_8$)cycloalkenyl, phenyl or benzyl.

10. A compound, method, use or composition as claimed in claim 9 wherein $R_3$ is methyl, ethyl, n-propyl, n-butyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxethyl, 2-carboxyethyl, 2-methylcarbamoylethyl, 2-carbamoylethyl, or 4-aminobutyl.

11. A compound, method, use or composition as claimed in claim 9 wherein $R_3$ is tert-butyl, iso-butyl, benzyl, isopropyl or methyl.

12. A compound, method, use or composition as claimed in in any of the preceding claims wherein $R_4$ is methyl.

13. A compound, method, use or composition as claimed in in any of the preceding claims wherein in the group $R_5$, m is 1, and $Alk^1$ is -($CH_2$)- or -($CH_2CH_2$)-.

13. A compound, method, use or composition as claimed in any of the preceding claims wherein, in the group $R_5$, Z is a cyclopentyl, cyclohexyl, phenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2-or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranyl, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring any of which may optionally be substituted by

hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, methyl, ethyl, trifluoromethyl, fluoro, chloro, amino, methylamino, or dimethylamino.

14. A compound as claimed in claim 1, a method as claimed in claim 2 or claim 3, the use as claimed in claim 4 or a composition as claimed in claim 5 wherein the compound is one specifically named and/or exemplified herein, or is the hydroxamate (Q represents a radical of formula -C(=O)NH(OH)) analogue thereof.